CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Clomazone

Chemical Code # 3537, **Tolerance #** 51878
SB 950 # New A.I.

Original: 2/25/02
Revised: 4/25/02

I. DATA GAP STATUS

Combined, rat:	Data gap, no adverse effect indicated[1]
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, possible adverse effect indicated[1]
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Study not required at this time

Toxicology one-liners are attached.

All record numbers through 186574 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T190437A
Revised by P. Leung, 4/25/02

[1] The rat and mouse combined chronic and oncogenicity feeding studies are unacceptable. There was a possible adverse chronic effect noted in the mouse study. A tier I chronic dietary exposure risk assessment for clomazone using DEEM (Version 7.76) with 1994-1998 consumption data was conducted by the registrant (FMC Corporation, Document 51878-049, Record # 186523). It assumed 100% of the crop was treated and that the residue levels were equal to the tolerance levels. The critical NOEL of 4.3 mg/kg/day was obtained from the two year rat chronic feeding study. With an uncertainty factor of 100, the chronic reference dose was calculated to be 0.043 mg/kg/day. All of the population groups examined had exposures less than 1% of the chronic reference dose (total US population: 0.246%, non-nursing infants: 0.872%, children 1 to 6 years old: 0.510%). USEPA did not consider drinking water to present a significant exposure to

clomazone: “EPA concludes with reasonable certainty that residues of clomazone in drinking water (when considered along with other sources of chronic exposure for which EPA has reliable data) would not result in unacceptable levels of chronic aggregate human health risk estimates.”[2] Repeating the combined rat chronic/oncogenicity and the mouse oncogenicity using higher doses would provide lower or less conservative estimate of risk.

[2] U.S. Environmental Protection Agency: Clomazone; Pesticide Tolerances for Emergency Exemptions, Federal Register Volume 64, No. 238, page 69409-69415, December 13, 1999.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

006; 182596; “Ninety Day Subchronic Toxicity Dietary and Twenty-Four Month Chronic Toxicity and Oncogenicity Dietary Study in Rats Utilizing FMC 57020 Technical”; (L.D. Morrow; Toxigenics, Inc., Decatur, IL; Study No. 410-0816; 7/10/84); One hundred twenty CD outbred rats/sex/group were dosed in the diet with 0, 20, 100, 500, 1000 and 2000 ppm of FMC 57020 Technical (Ref. No. E1756-146, purity: 88.8%) for 24 months ((M: 0, 0.89, 4.41, 22.0, 44.1, and 88.9 mg/kg/day, F: 0, 1.14, 5.70, 28.7, 58.4, and 115.6 mg/kg/day). The same number of animals/sex/group were dosed with 4000 or 8000 ppm of the test material for 16 weeks (M: 273.0 and 552.2 mg/kg/day, F: 319.3 and 629.5 mg/kg/day). Ten animals/sex/group were euthanized and examined at the 1 and 2 month intervals. Twenty animals/sex/group were euthanized and examined at 3 months. The surviving animals were maintained for the chronic feeding study. The mean body weights of the 8000 ppm males ($p<0.01$) and the 4000 and 8000 ppm females ($p<0.01$) were less than that of the control animals during the 1st 16 weeks. Mean food consumption was reduced for the 8000 ppm males and the 4000 and 8000 ppm females over that time period ($p<0.05$). No treatment-related signs were noted. There were no treatment-related effects indicated by the hematology results. In the clinical chemistry, the mean total cholesterol levels in the serum were elevated for the 8000 ppm males and females at 1, 2, and 3 months ($p<0.01$). The mean levels for the 1000 ($p<0.01$) and 4000 ($p<0.05$) ppm females were elevated at 3 months as well. There were no treatment-related effects in the urinalysis data. The mean liver weight was increased above that of the control for both sexes at 2000 ppm and above and for the 500 ppm males at 3 months. No effects on liver weight were noted at 6 months and thereafter. In the histopathology examination, diffuse, centrilobular megalocytosis was noted in the liver for the 2000 ppm males (minimal: 2/20) and the 8000 ppm males (minimal: 4/20, mild: 1/20) and 8000 ppm females (minimal: 8/20, mild: 11/20) at 3 months. (Note: the 4000 ppm animals were not examined). No treatment-related effects on the liver were noted thereafter. **No adverse effect indicated. Reported Chronic NOEL:** (M/F) 2000 ppm (M: 88.9 mg/kg/day, F: 115.6 mg/kg/day) (no effects on the highest dose tested); **No oncogenicity apparent; Study unacceptable** (urinalysis was not adequately performed, eyes did not receive an ophthalmology examination, maximum tolerated dose not achieved)**.** (Moore, 12/20/01)

CHRONIC TOXICITY, RAT

See the Combined, Rat.

CHRONIC TOXICITY, DOG

** 011, 012; 182601, 182602; “ One-Year Chronic Oral Toxicity Study in Dogs According to EPA Guidelines” (Reno, F.E., Hazleton Laboratories America, Inc., Madison, WI, FMC Study No. A82-759, HRI Study No. 6124-101, 6/22/84). 831. FMC 57020 Technical (Lot No. Ref. E1756-146, purity = 88.8%) was admixed to the feed (plus 2% corn oil) and fed to 6 beagle dogs per sex per dose at dose levels of 0 (untreated diet), 100, 500, 2500, or 5000 (reduced from 7500 ppm at Day 8) (0, 19.4, 97.8, 493.9, 1038.4 mg/kg/day, respectively, for males and 0, 20.7, 104.0, 529.4, 1011.9 mg/kg/day, respectively, for females, (values calculated by the reviewer)) for 1 year (2 animals per sex per dose were sacrificed after 3 months of treatment). No animals died. At the high dose level, decreased body weight and low food consumption were observed in the first 2

weeks of treatment; therefore, the high dose level was decreased from 7500 ppm to 5000 ppm. A treatment-related increase in serum cholesterol levels in both sexes at 2500 and 5000 ppm at all intervals was observed. A treatment-related increase in mean relative liver weight at 2500 and 5000 ppm in males (both interim and terminal sacrifice animals) and females (interim sacrifice animals only) was observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 97.8 mg/kg/day (500 ppm) and NOEL (F) = 104.0 mg/kg/day (500 ppm) (values calculated by the reviewer) based on increased serum cholesterol levels and increased mean relative liver weights. **Acceptable**. (Corlett and Leung, 11/27/01)

ONCOGENICITY, RAT

See the Combined, Rat

ONCOGENICITY, MOUSE

008; 182598; "Ninety-Day Subchronic Toxicity Dietary and Twenty-Four Month Chronic Toxicity and Oncogenicity Dietary Study in Mice Utilizing FMC 57020 Technical"; (L.D. Morrow; Toxigenics, Inc., Decatur, IL; Study No. 410-0817; 6/25/84); One hundred twenty CD-1 mice/sex/group were treated in the diet with 0, 20, 100, 500, 1000, 2000 of FMC 57020 Technical (Ref. No. E1756-146, purity: 88.8%) for up to 24 months (M: 0, 2.97, 15.0, 75.4, 147.4, 299.1 mg/kg/day, F: 0, 3.70, 18.5, 92.9, 190.8, 376.2 mg/kg/day). An additional 120 animals/sex/group were fed 4000 or 8000 ppm of the test material for up to 16 weeks prior to being euthanized (M: 751.8, 1660 mg/kg/day, F: 1033, 2205 mg/kg/day) Ten animals/sex/group were euthanized and grossly examined at the 1 and 2 month intervals. Twenty animals/sex/group were euthanized and examined histologically at 3 months. An additional 10 animals/sex/group each were euthanized and examined histologically after 6, 12 and 18 months of treatment. The surviving animals were euthanized at 24 months. There was no treatment-related effect upon clinical signs, mean body weight or food consumption. There were no treatment-related effects indicated by the hematology results or clinical chemistry. The mean absolute and relative liver weights was increased above that of the control for both sexes at 4000 ppm and above ($p<0.01$) after 3 months of treatment. Except for an increase in the mean relative weight for the females in the 2000 ppm group at 6 months ($p<0.05$), no other effect on liver weights was noted. In the histopathology examination at 3 months, diffuse, centrilobular megalocytosis was noted in the livers of the 8000 ppm males (minimal: 4/20, mild: 4/20, moderate: 1/20) and a minimal response in two males in the 2000 ppm group. At 6 months, hepatocellular cytomegaly was reported for males in the 1000 and 2000 ppm groups (0: 0/10, 1000: 2/10, 2000: 5/10). At 12 months, hepatocellular cytomegaly was noted for the 2000 ppm group males (0: 0/10, 2000: minimal, 1/10, mild, 2/10). The females in the 2000 ppm group exhibited hepatic necrosis (0: minimal, 1/10, 2000: mild, 3/10, severe, 1/10). At 18 months, hepatocellular cytomegaly was noted males in the 2000 ppm group (0: 0/10, 2000: 2/10) and hepatic necrosis was noted for the 2000 ppm females (0: 0/10, 2000: 5/10). At 24 months, the 2000 ppm males exhibited an increased incidence of hepatocellular cytomegaly (0: 0/20, 2000: 3/22) and vaculoar hepatocellular degeneration (0: 0/20, 2000: 5/22). Lymphoid hyperplasia was noted in the thymus of the 1000 and 2000 ppm females (0: 2/20, 1000: 12/23, 2000: 10/24). An increased incidence of gastric adenoma and carcinoma combined was noted for the 1000 and 2000 ppm males (adenoma, 0: 1/20, 1000: 2/23, 2000: 1/22, carcinoma, 0: 0/20, 1000: 0/23, 2000: 2/22). This incidence, however, was not statistically significant using the Fisher's exact test. **Possible adverse effect:** hepatocellular necrosis. **Chronic (M/F):** 1000 ppm ((M)147.4 mg/kg/day, (F) 190.8 mg/kg/kg) (based on incidence of hepatocellular cytomegaly noted for the 2000 ppm males and hepatic necrosis in the 2000 ppm females); **No oncogenicity evident. Study unacceptable**, not upgradeable (ophthalmology and urinalysis examinations were not performed and maximal tolerated dose was not achieved for oncogenicity). (Moore, 1/24/02)

REPRODUCTION, RAT

** 017; 182610; "Two Generation Reproduction Study in Albino Rats with FMC 57020 Technical"; (C.M. Salamon; Toxigenics, Inc., Decatur, IL; Study No. 450-1095; 6/12/84); Twenty five Sprague-Dawley rats/sex/group were fed in the diet 0, 100, 1000, 2000 or 4000 ppm of FMC 57020 Technical (Ref. No. E1756-146, purity: 88.8%) for two generations (a.i. uptake, determined during

premating only, F0 generation, (M) 0, 7.08, 69.3, 138.3, 274.7 mg/kg/day, (F) 0, 8.84, 83.9, 157.9, 303.2 mg/kg/day, F1 generation, (M) 0, 8.36, 82.1, 163.5, 331.2 mg/kg/day, (F) 0, 9.25, 88.3, 174.0, 353.7 mg/kg/day). In the 1st generation, the F0 parents were treated for 8 weeks in the premating period, up to 3 weeks for F1a mating, 3 weeks each for F1a gestation and lactation, 1 week interlude, up to 3 weeks for F1b mating, and 3 weeks each for F1b gestation and lactation. The F1 parental generation was treated with the test material for 11 weeks in the premating period and for the same time periods as the F0 generation during the production of the F2a and F2b litters. The females in the 2000 and 4000 ppm groups of both the F0 and F1 generations had lower mean body weights than did the respective controls at the end of the premating period ($p<0.01$ or $p<0.05$). At various time points during the gestation periods of the two generations, females in the 2000 and 4000 ppm groups had lower mean body weights as well ($p<0.01$ or $p<0.05$). Mean relative liver weights for the 4000 ppm males and females in both the F0 and F1 generations and the 2000 ppm females in the F1 generation were greater than those of the control ($p<0.01$ or $p<0.05$). There were no treatment-related effects on mating parameters, mean litter size or pup viability. Mean body weights for the pups in the 2000 and 4000 ppm treatment groups were less than those of the controls at various time points during the lactation periods for both the F1 and F2 progeny ($p<0.01$ or $p<0.05$). **No adverse effects indicated**. **Parental NOEL:** 1000 ppm ((M) 69.3 mg/kg/day, (F) 83.9 mg/kg/day) (based upon lower mean body weights for the animals in the 2000 ppm treatment group), **Reproductive NOEL:** 4000 ppm ((M) 331.2 mg/kg/day, (F) 353.7 mg/kg/day) (based no treatment-related effects for the highest dose tested), **Developmental NOEL:** 1000 ppm ((M) 69.3 mg/kg/day, (F) 83.9 mg/kg/day) (based upon lower mean body weights for pups in the 2000 ppm treatment group). **Study acceptable.** (Moore, 2/1/02)

TERATOLOGY, RAT

** **014, 049; 182604, 186574;** "Teratology Study in Rats with FMC 57020 Technical"; (C. Freeman; FMC Toxicology Laboratory, Somerville, NJ; Study No. A83-1142; 6/29/84); Twenty five mated Sprague-Dawley females/group were dosed by oral gavage with 0, 100, 300 or 600 mg/kg of FMC 57020 Technical (ref. no. E 1756-146, purity: 88.8%) in corn oil from day 6 of gestation through day 15 of gestation. Two of the females in the 600 mg/kg group were misdosed on day 11 and died. One of the females in the 300 mg/kg group also was misdosed but survived. Her data was not included in the tabulation of the study results. There were no treatment-related effects on the mean body weights. Mean food consumption for the 600 mg/kg females was less than that of the control animals over the treatment period ($p<0.01$). The mean body weights of the female fetuses in the 600 mg/kg group were less than that of the control fetuses ($p<0.05$). The number of litters which exhibited delayed ossification of the manubrium and sternabrae was increased for the 300 and 600 mg/kg groups (manubrium, 0: 0/25, 300: 5/23, 600: 4/23, sternabrae, 0: 0/25, 300: 4/23, 600: 5/23, ($p<0.05$)). **Possible adverse effect:** delayed development of the fetuses; **Reported Maternal NOEL:** 600 mg/kg (based upon the lack of a treatment-related effect for the highest group tested), **Reported Developmental NOEL:** 100 mg/kg (based upon delayed ossification noted for the fetuses in the 300 mg/kg treatment group); **Study** rereviewed with supplemental data and was found to be **acceptable** (Moore, 12/31/01; upgraded, Leung, 4/24/02).

TERATOLOGY, RABBIT

** 013, 049; 182603, 186574; "A Teratology Study in Rabbits with FMC 57020"; (D.E. Rodwell; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-81157; 9/14/82); Eighteen artificially inseminated New Zealand White female rabbits were dosed by oral gavage with 0, 30, 240 or 1000 mg/kg of FMC 57020 (ref. E1756-146; purity: 88.8%) in 1% aqueous methylcellulose (MC) from day 6 through day 18 of gestation. The dose administered to the 1000 mg/kg group was reduced to 700 mg/kg on day 13 due to the excessive toxic effects noted at the time. The mean body weight gain of the females in the 1000/700 mg/kg group was less than that of the control over the treatment period ($p<0.01$). There were no apparent treatment-related effects upon the development of the fetuses. **No adverse effect indicated. Reported Maternal NOEL:** 240 mg/kg (based upon the loss in mean body weight gain exhibited by the 1000/700 mg/kg treatment group), **Reported Developmental NOEL:** 700 mg/kg (based upon the lack of effects

upon the highest dose tested); Study rereviewed with supplemental data and found to be **acceptable**). (Moore, 12/27/01; upgraded, Leung, 4/24/02)

GENE MUTATION

015; 182606; "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenesis Assay"; (S. R. Haworth; EG&G Mason Research Institute, Rockville, MD; Study No. 013-679-407-1; 2/29/80); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated for 48 hours at 37° C with FMC 57020 Technical (lot no. E249-1; purity: not reported) at treatment levels ranging from 0 to 4 ul/plate with and w/o activation. One trial was performed with triplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study unacceptable**, not upgradeable (positive controls were not included with 3 of the strains under conditions of activation)**.** (Moore, 1/3/02)

016; 182609; "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenesis Assay (Ames Assay)"; (S.R. Haworth; EG&G Mason Research Institute, Rockville, MD; Study No. 013-522-700-1; 1/20/82). *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated with FMC 57020 Technical (lot no. E-1382-95, purity not reported) at concentrations ranging from 0 to 600 ug/plate for 48 hours at 37° C under conditions of activation and non-activation. One trial was performed with triplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study unacceptable**, not upgradeable (purity of the test material was not reported, mutagenicity of the test material was not adequately assessed under conditions of activation). (Moore, 1/7/02)

** 014; 182605; "*Salmonella*/ Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)"; (S.R. Haworth and T.E. Lawlor; Microbiological Associates, Bethesda, MD; Study No. T2467.501; 6/14/84); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated for 48 hours at 37° C with FMC 57020 Technical (lot no. E3376-112; purity: 93.4% initially, 92.4% upon reassay) at treatment levels ranging from 0 to 5 mg/plate with and w/o activation. One trial was performed with triplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 1/3/02)

018; 182611; "CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation"; (A. Thilagar; Microbiological Associates, Bethesda, MD; Study No. A83-1143; 6/6/84); Chinese Hamster Ovary (CHO-K_1-BH_4) cells were exposed to FMC 57020 Technical (lot no. E1756-146, purity: 88.8%) at concentrations ranging from 0 to 600 ug/ml for 5 hours at 37° C with and w/o activation. One trial was performed with duplicate cultures for each treatment level. However, cultures were pooled during the assay such that each treatment level was represented by a single culture. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related statistically significant increase in the mutant frequency of the treated cells. **No adverse effect indicated. Study unacceptable** not upgradeable due to the lack of a replicate assay and the pooling of cultures during the assay**.** (Moore, 2/4/02)

CHROMOSOME EFFECTS

** 015, 048; 182607, 186195; " *In Vivo* Cytogenetic Assay of FMC 57020 Technical in Rats"; (D.L. Putman; Microbiological Associates, Bethesda, MD; Study No. T1839.102; 12/30/82); Five male Sprague-Dawley rats/group were dosed by oral gavage daily for 5 days with 0, 200, 667 or 2000 mg/kg of FMC 57020 Technical (lot no. E1756-146-20, purity: 88.8%). Following the fifth dose, the animals were treated by ip injection of colchicine (1 mg/kg) and euthanized. A positive control of 5 males was treated by ip injection with 0.5 mg/kg of triethylenemelamine once 24 hours prior to being euthanized. The bone marrow was extracted from the femurs and evaluated for the incidence of chromosomal aberrations. Fifty cells/animal were scored for chromosomal aberrations. There was no treatment-related increase in the incidence of chromosomal

aberrations. Positive control was functional. **No adverse effect indicated.** Study rereviewed with supplemental data and was found to be **acceptable.** (Moore, 1/4/02; upgraded, Leung, 4/24/02).

DNA DAMAGE

** 015; 182608; "Unscheduled DNA Synthesis Assay of FMC 57020 Technical in Rat Hepatocytes"; (A. Thilagar; Microbiological Associates, Bethesda, MD; Study No. T2107.380; 9/19/83); Primary rat hepatocyte cultures were exposed to FMC 57020 Technical (lot no. E1756-146-20, purity: 88.8%) at concentrations ranging from 0.001 to 0.10 ul/ml for 18 hours at 37° C. Solvent and positive (2-acetylaminofluorene, 2 and 20 ug/ml) controls were included in the assay. There was one trial with 3 cultures/treatment level. Twenty five cells/culture were evaluated for net nuclear grain count. Positive controls were functional. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated. Study acceptable.** (Moore, 1/7/02)

NEUROTOXICITY

Study not submitted.

SUBCHRONIC STUDIES

51878-004; 182594; "Ninety-Day Final/Three Month Interim Report: Ninety Day Subchronic Toxicity Dietary and Twenty-Four Month Chronic Toxicity and Oncogenicity Dietary Study in Rats Utilizing FMC 57020 Technical"; (L.D. Morrow and G.D. Taylor; Toxigenics, Inc., Decatur, IL; Study No. 410-0816; 4/12/83); One hundred twenty CD outbred rats/sex/group were dosed in the diet with 0, 20, 100, 500, 1000, 2000, 4000 or 8000 ppm of FMC 57020 Technical (Ref. No. E1756-146, purity: 88.8%) for 90 days (M: 0, 1.40, 7.80, 35.3, 69.7, 138.8, 278.8, 562.9 mg/kg/day, F: 0, 1.67, 8.38, 42.6, 84.7, 163.3, 324.2, 638.1 mg/kg/day). Ten animals/sex/group were euthanized and examined at the 1 and 2 month intervals. Twenty animals/sex/group were euthanized and examined at 3 months. The surviving animals were maintained for the chronic feeding study. The mean body weights of the 8000 ppm males ($p<0.01$) and the 4000 and 8000 ppm females ($p<0.01$) were less than that of the control animals. Mean food consumption was reduced for the 8000 ppm males and the 4000 and 8000 ppm females over the course of the study ($p<0.05$). No treatment-related signs were noted. There were no treatment-related effects indicated by the hematology results. In the clinical chemistry, the mean total cholesterol levels in the serum were elevated for the 8000 ppm males and females at 1, 2, and 3 months ($p<0.01$). The mean levels for the 1000 ($p<0.01$) and 4000 ($p<0.05$) ppm females were elevated at 3 months as well. There were no treatment-related effects in the urinalysis data. The mean liver weight was increased above that of the control for both sexes at 2000 ppm and above and for the 500 ppm males. In the histopathology examination, diffuse, centrilobular megalocytosis was noted in the liver for the 2000 ppm males (minimal: 2/20) and the 8000 ppm males (minimal: 4/20, mild: 1/20) and 8000 ppm females (minimal: 8/20, mild: 11/20). (Note: the 4000 ppm animals were not examined). Target organ: liver; **No adverse effect indicated. Reported NOEL:** (M/F) 1000 ppm (M: 69.7 mg/kg/day, F: 84.7 mg/kg/day) (based upon the increased mean liver weight of the 2000 ppm treatment group); **Study unacceptable** (urinalysis was not adequately performed and the eyes did not receive an ophthalmology examination) **.** (Moore, 12/17/01)

010; 182600; "Twenty-Eight Day Oral Range-Finding Study in Mice Utilizing FMC 57020" (Morrow, L.D., Toxigenics, Inc., Decatur, IL, FMC Study A81-612, Toxigenics' Study 410-0744, 11/11/82). FMC 57020 Technical (Lot no. E1382-95, purity = 87.9%) was admixed to the feed and fed to 10 CD-1 mice per sex per dose at dose levels of 0 (untreated diet), 2000, 4000, 8000, 16000, 24000, or 50000 ppm (0, 433, 922, 1927, 3727, 5153, not determined mg/kg/day, respectively, for males, and 0, 525, 1140, 2295, 4764, 4590, 4311 mg/kg/day, respectively, for females) for 28 days. All animals at 50000 ppm died within 10 days; no other animals died. Weakness, staggering gait, perineum stained yellow/brown, and ptosis were observed in the animals at 50000 ppm prior to death. A treatment-related decrease in mean body weight at 16000 and 24000 ppm in both sexes was observed. A treatment-related increase in mean relative liver weight at 8000, 16000, and 24000 ppm in both sexes was observed. **No adverse**

effects. NOEL (M)= 922 mg/kg/day (4000 ppm) and NOEL (F) = 1140 mg/kg/day (4000 ppm) based on increased mean relative liver weights. **Supplemental** (animals were dosed for only 28 days and no histopathology was performed). (Corlett, 11/6/01)

51878-007; 182597; "Ninety-Day Final/Three Month Interim Report: Ninety Day Subchronic Toxicity Dietary and Twenty-Four Month Chronic Toxicity and Oncogenicity Dietary Study in Mice Utilizing FMC 57020 Technical"; (L.D. Morrow; Toxigenics, Inc., Decatur, IL; Study No. 410-0817; 4/11/83); One hundred twenty CD-1 mice/sex/group were treated in the diet with 0, 20, 100, 500, 1000, 2000, 4000 or 8000 ppm of FMC 57020 Technical (Ref. No. E1756-146, purity: 88.8%) for 90 days (M: 0, 3.79, 19.5, 97.7, 188.2, 370.8, 761.0, 1689 mg/kg/day, F: 0, 5.26, 25.9, 126.4, 263.2, 522.3, 1049, 2233 mg/kg/day). Ten animals/sex/group were euthanized and examined at the 1 and 2 month intervals. Twenty animals/sex/group were euthanized and examined at 3 months. The surviving animals were maintained for the chronic feeding study. There was no treatment-related effect upon clinical signs, mean body weight or food consumption. There were no treatment-related effects indicated by the hematology results or clinical chemistry. The mean liver weight was increased above that of the control for both sexes at 4000 ppm and above ($p<0.01$). In the histopathology examination, diffuse, centrilobular megalocytosis was noted in the liver for the 8000 ppm males (minimal: 4/20, mild: 4/20, moderate: 1/20). (Note: the 4000 ppm animals were not examined). Target organ: liver; **No adverse effect indicated. Reported Subchronic NOEL:** (M/F) 2000 ppm (M: 370.8 mg/kg/day, F: 522.3 mg/kg/day) (based upon the increased mean liver weights for the 4000 ppm animals). **Study unacceptable,** not upgradeable (the eyes did not receive an ophthalmology examination and only a limited number of parameters were assayed in the clinical chemistry) (Moore, 12/26/01)

009; 182599; "Twenty-Eight Day Oral Range-Finding Study in Dogs" (Reno, F.E., Hazleton Raltech, Inc., a Subsidiary of Hazleton Laboratories America, Inc., Madison, WI, FMC Study No. A82-758, HRI Study No. 6124-100, 2/4/83). FMC 57020 Technical (Lot no. E1756-146, purity = 88.8%) was admixed to the feed and fed to 2 beagle dogs per sex per dose at dose levels of 0 (untreated diet), 100, 1000, 2500 (reduced from 10000 ppm at day 9), or 5000 ppm (0, 2.5, 25, 62.5/250, 125 mg/kg/day, respectively, calculated by the reviewer) for 28 days. No animals died. Low food consumption was observed at 2500/10000 and 5000 ppm in both sexes. A treatment-related decrease in mean body weight at 2500/10000 and 5000 ppm in both sexes was observed. A treatment-related increase in mean relative liver weight at 1000, 2500/10000 and 5000 ppm in males and at 2500/10000 and 5000 ppm in females was observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 2.5 mg/kg/day (100 ppm) and NOEL (F) = 25 mg/kg/day (1000 ppm) (values calculated by the reviewer) based on increased mean relative liver weights. **Supplemental** (animals were dosed for only 28 days and no ophthalmology was performed). (Corlett, 11/9/01)

(Dermal)

048; 186196; "Clomazone Technical 28-Day Repeated-Dose Dermal Study in Rats" (Watt, B. and Freeman, C., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A2001-5436, 2/13/02). 822. Clomazone Technical (Reference No. PL01-0346, purity = 92.7%) was applied to the clipped dorsal skin of 10 Sprague-Dawley CD rats per sex per dose at dose levels of 0 (tap water only) or 1000 mg/kg/day for 6 hours per day, 5 days per week for 4 consecutive weeks. No mortalities occurred. No clinical signs or local irritation effects were observed. Body weight, food consumption, ophthalmology, serum chemistry, hematology, and organ weight data revealed no treatment-related effects. FOB and motor activity assessments revealed no treatment-related effects. Necropsy revealed no treatment-related abnormalities. Microscopic examination revealed an increase in severity (males) and incidence (females) of epidermal hyperplasia in the treated skin. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F, skin) < 1000 mg/kg/day based on an increase in severity (males) or incidence (females) of epidermal hyperplasia in the treated skin. **Acceptable**. (Corlett, 4/15/02)

METABOLISM STUDIES

Metabolism, Rat

** 018; 182612; "Rat Balance Study and Tissue Distribution of Methylene ^{14}C-Labeled FMC 57020"; (S. Selim; Primate Research Institute, New Mexico State University, Holloman AFB, NM; Study No. FM-124r; 3/22/84); Sprague-Dawley (CD, Crl (SD)Br) rats of both sexes were dosed with 3, 5, or 900 mg/kg of Methylene ^{14}C-Labeled FMC 57020 (2[(2'-chlorophenyl)-^{14}C-methyl]-4,4-dimethyl-3-isoxazolidinone, lot no. E678-128; radiopurity: 99.8%; specific activity: 26.81 mCi/mmol). In Study A, two rats/sex were orally dosed by gavage with 5 mg/kg of the test material and expired air was collected for up to 24 hours. In the remaining studies, 5 animals/sex/group were dosed. In Studies B and C, the animals received a single oral dose of 5 and 900 mg/kg of the test material, respectively. In Study D, each animal was dosed intravenously with 3 mg/kg of the test material. In Study E, the animals received 14 doses, once per day for 2 weeks, of unlabeled FMC 57020 (purity: 99.0%). In Study B, C, D and E, urine and feces samples were collected periodically for 7 days. After 7 days, the animals were euthanized and radioactivity in the tissues was determined. Excretion of radiolabeled CO_2 constituted less than 0.01% of the recovered dose. The primary pathway of excretion was in the urine with a range of 63.4 to 82.9% of the administered dose in the urine. Recovery in the feces ranged from 15.1 to 38.7% of the administered dose. At 7 days post-dose, aggregate residue levels in the tissues and carcass ranged from 0.08 to 0.17% of the administered dose. The amount dosed or frequency of the dosing did not affect the excretory profile. A biliary excretion study was not performed to evaluate whether any of the material in the feces may have absorbed prior to excretion. **Study acceptable.** (Moore, 2/11/02)

018; 182613; "Metabolism of Methylene ^{14}C-Labeled FMC 57020 in Rats**";** (J.Wu and R.A. Robinson; FMC Agricultural Chemical Group, Princeton, NJ**;** Study No. P-0898; 6/1884); Sprague-Dawley (CD, Crl (SD)Br) rats of both sexes were dosed with 3, 5, or 900 mg/kg of Methylene ^{14}C-Labeled FMC 57020 (2[(2'-chlorophenyl)-^{14}C-methyl]-4,4-dimethyl-3-isoxazolidinone, lot no. E678-128; radiopurity: 99.8%; specific activity: 26.81 mCi/mmol) by oral gavage or intravenous injection in accordance with the protocol set forth in the previously reviewed metabolism study (record no. 182612). Radiolabeled compounds were recovered from the urine and feces samples and analyzed by HPLC, TLC, GC/MS and NMR in order to identify various metabolites of the test material. Pooled 24 hour and 48 hour urine and feces samples were extracted to yield free metabolites and enzyme- and acid-released aglycone fractions. Hydroxylation of the phenyl and/or isoxazolidinone rings was the most common alteration of the parent compound which was observed. The distribution of the hydroxylated metabolites varied somewhat in relation to the dosing regimen and dosing level used. Conjugated metabolites were observed in both the urine and the feces. Little of the parent compound was recovered. **Supplemental Study.** (Moore, 2/13/02)

018; 182614; "Identification of Metabolites in Urine and Feces of Rats Dosed with ^{14}C-FMC 57020"; (J. Wu and R.A. Robinson; FMC Agricultural Chemical Group, Princeton, NJ; Study No. P-0897; 6/14/84, reissued, 7/23/84); Four Sprague-Dawley rats/sex were treated by oral gavage with a single dose of 50 mg/kg of a mixture of Methylene-^{14}C FMC 57020 (ref. no. E1539-15, specific activity: 26.85 mCi/mmol, radiochemical purity: 99.3%) and Carbonyl-^{14}C FMC 57020 (ref. no. E678-147, specific activity: 27.98 mCi/mmol**,** radiochemical purity: 99.3%). Radiolabeled compounds were recovered from the urine and feces samples and analyzed by HPLC, TLC, GC/MS and NMR in order to identify various metabolites of the test material. Twelve metabolites were recovered and identified. Hydroxylation of the phenyl and/or isoxazolidinone rings was the most common alteration of the parent compound which was observed with some evidence of glucuronide and sulfate conjugation. The structure of each metabolite is listed below. No quantification of the metabolites was performed. **Study supplemental.** (Moore, 2/14/02)